Nicotine Pharmacokinetics

Introduction

Nicotine is considered to be the major pharmacologically active component of tobacco, and therefore general aspects in the pharmacokinetics of nicotine should be taken into consideration when discussing the pharmacological effects of nicotine.

Administration

Administration of nicotine in the human situation is usually done by smoking tobacco products like pipe tobacco, cigars, and cigarettes, by exposure to environmental tobacco smoke, by the use of smokeless tobacco products like snuff, by the use of, e.g, nicotine chewing gum, nicotine nasal spray, nicotine patches (medicational use), and due to dietary sources (e.g. potatoes, tomatoes, eggplants, tea) (e.g. Davis et al., 1991).

Absorption

Rate of absorption and distribution profoundly affects the magnitude of pharmacological effects of nicotine (Benowitz et al., 1990).

Much of the nicotine present in tobacco is not absorbed. Losses: smoking tobacco products by pyrolysis and sidestream smoke; use of smokeless tobacco by expectoration.

Machine determined delivery of nicotine does not correlate well with the amount of nicotine absorbed by smokers (Benowitz et al., 1993; Ebert et al., 1983; Benowitz & Jacob 1984b; Feyerabend et al., 1985; Benowitz et al., 1986; Kozlowki et al., 1988; alles [sec., 0])

The commonly sites of nicotine absorbtion are the lungs, buccal mucosa, nasal mucosa, gastrointestinal tract, and skin.

Lungs: Nicotine is rapidly absorbed from inhaled smoke reaching the systematic circulation at a rate comparable with intravenous administration (Russel and Feyerabend, 1978; [sec., 10])

Smokers maintain relatively constant levels of nicotine in the body (Benowitz et al., 1982b [sec., 10, p220])

There is considerable experimental evidence to suggest that smokers have the ability (and also try) to maintain a steady state concentration of nicotine in the body by modifying the way in which cigarettes are smoked - such as the depth of inhalation or frequences of puffs - for compensation [10, p220].

Buccal mucosa: Absorption is highly dependent on the pH. It is well absorped at higher pH (8.5, unionised form of nicotine) like smoke from air-cured tobacco (from pipes, cigars). Cigarette smoke (flue-cured tobacco) is acidic (pH 5.5) that means that nicotine is in its ionized form and little absorption takes place from such smoke held in the mouth [10, p220 ff].

Nasal mucosa: Nicotine from dry snuff or from smoking cessation spray is rapidly absorbed from the nasal mucosa. With dry snuff plasma concentration comparable with those reached by cigarette smoking can be achieved (Russel et al., 1980 [sec., 10])

Gastrointestinal tract: Absorption from the stomach is limited due to the acid pH whereas the absorption in the intestine is extensive. However, of the nicotine absorped only 25 to 30 % reaches the systemic circulation because of an extensive first-pass metabolism of nicotine after uptake of nicotine by the GI-tract [10, p220 ff].

Skin: Absorption by the skin is associated with accidental poisoning, e.g., by tobacco plant material, as well as with the dermal application by nicotine patches used as an adjuvant to smoking cessation. Transdermal absorption is slow, reaching peak plasma concentrations after 90 min (Rose et al., 1984 [10, p222]).

Distribution

Volume of distribution: 290 l (2 mg/kg*min, 90 min) [0]
ca. 200 l (0.5 mg/kg*min, 90 min) [0]
(2 mg/kg*min, 90 min) [0]

Metabolism

Metabolism of nicotine affects the elimination of nicotine in and from the body, thus affecting the pharmacology of nicotine by lowering its levels in the body.

Metabolites of nicotine may be pharmacologically active (Clark et al., 1965).

Rate of nicotine metabolism is quite variable between individuals (Benowitz et al., 1982, [sec., 0]; Byrd et al., 1992).

Different initial pathways of nicotine metabolism, various metabolizing enzyme systems involved.

Similar pattern in urinary nicotine metabolites are found in the same individuals following smoking or after transdermal administration [0]

In vitro studies and ex vivo studies on isolated organs show that metabolism of nicotine takes place in liver, lung, and kidney.

Endogenous factors influencing nicotine metabolism

Genetic regulation of enzymes: Genetic polymorphism is described for various isoenzymes of cytochrome P450 and of flavin containing monooxigenases, enzyme systems strongly involved in the metabolism of nicotine.

Developmental regulation:

age: mouse: (Stalhandske, 1977 [10, p230])

rat: C- and N-oxidation pathway decreased with increasing age (40 to 100d). (Kyerematen et al., 1988a [10, p.230])

human: In smokers, the ratio of urinary excretion of cotinine to nicotine-N'-oxide decreased with increasing age (Klein & Gorrod, 1978 [10, p230]).

sex: rat: (Schepers et al. 1993)

macaque: lower nicotine clearance in females (Seaton et al., [10, p231]

human: Female smokers excreted more unchanged nicotine, less cotinine (and more nicotine plus cotinine?) than male smokers (Beckett et al., 1971; [10, p230]).

Total plasma clearance of nicotine (normalized to body weight) was lower in femals (Benowitz and Jacob, 1984 [10, p230/31]).

No differences in the ratio of urinary excretion of cotinine to nicotine-N'-oxide (Klein & Gorrod, 1978 [10, p230]).

species: Species differences in nicotine metabolism are found. The major metabolites excreted in the urine are nicotine-N'-oxide in the guinea pig and rat (Nwosu and Crooks, 1988; Schepers et al., 1993) and trans-3'-hydroxycotinine in the human (Neurath et al., 1988; Curvall; Benowitz; Byrd; ...) and in the hamster (Nwosu and Crooks, 1988).

strain: Significant differences were found in pharmacokinetics of nicotine, cotinine, and nicotine-N'-oxide in 3 inbred mice strains (Petersen et al., 1984; [10, p.233].

ethnic groups: There is some evidence that let suggest ethnic differences in nicotine disposition, e.g., in serum cotinine concentration [10, p233/34].

effects of diseases: little information, one study (Gorrod et al., 1974; [10]) show that the ratio cotinine to nicotine-N'-oxide was significantly higher in smokers with cancer of the urinary bladder than in smokers without bladder cancer. However, it is unclear whether this is an effect of disease, medical treatment, or genetic predisposition going along with the susceptibility for bladder cancer.

exogenous factors

ethanol: In a rat study it was shown that ethanol pretreatment (over 12 days) significantly lower the plasma levels of nicotine and cotinine. Furthermore, an increase of the apparent volume of distribution and total plasma clearance of nicotine as well as an increase of the apparent volume of distribution and production rate of cotinine was observed (Adir et al., 1980; [10, p237]).

Acute dose of ethanol shows an inhibitoring effect on the metabolism of nicotine. In rabbits, total plasma clearance was decreased whereas plasma concentrations of cotinine were unaffected. (rat, rabbit?, in vivo, in vitro, ex vivo?) (Schüppel & Domdey-Bette, 1987; Domdey-Bette & Schüppel, 1987; [10, p237]).

phenobarbital: mouse: enhanced metabolism of nicotine to cotinine (Stalhandske, 1970; [10]).

rats: increased hepatic first path effect on nicotine metabolism and inhibited formation of nicotine-N'-oxide (Foth et al., 1990; [10]

macaque: accelerated production of 8 nicotine metabolites (except of nornicotine and nicotine-N'-oxide) (Seaton et al., 1991; [10].

3-methylcholanthrene, β-naphthoflavone: no effect on nicotine metabolism in isolated rat lungs and liver (Foth et al., 1991; [10]).

Aroclor 1254: Nicotine metabolism in the rat is shifted from N- to C-oxidation pathway (Schepers et al., 1993).

further substances influencing nicotine pharmakokinetics: metyrapone, 1-octylamine, methimazole, N-hydroxyamphetamine, A-methylbenzylaminobenzotriazole, norbenzphetamine, cimetidine, ranitidine, carbimazole (all cited in [10, p239/240]).

tobacco: Substances in tobacco smoke could induce or inhibit nicotine metabolism [0].

Smoking may influence the rate of nicotine metabolism (Beckett et al., 1971), Kyerematen et al., 1982, Lee et al., 1987).

Nonsmokers metabolize nicotine more rapid than smokers: Jacob and Benowitz, 1993;

Both total and non-renal clearance of nicotine were increased (more rapid metabolism) in smokers after 7 day abstinence than after over-night abstinence (Lee et al., 1987; [0, 10 p242]). (In addition to inductive effect of TS also an inhibitoring effect?)

Smokers metabolize nicotine more rapid than nonsmokers: Kyerematen et al., 1982.

Terminal halflife of plasma nicotine significantly shorter in smokers than in nonsmokers (Kyerematen et al., 1983; [10, p241]).

Elimination halflife of nicotine was significantly shorter, elimination rate constant was elevated, volume of distribution was deminished in smokers compared to nonsmokers. No change in clearance and AUC by smoking! Elimination halflife of cotinine shorter in smokers than in nonsmokers. (Kyerematen et al., 1982, 1983; [10, p241]).

Faster urinary and plasma elimination of both nicotine and cotinine in smokers compaired to nonsmokers (Kyerematen et al., 1990b; [10, p241]).

Half life of cotinine in smokers has been shown to be shorter than in individuels exposed to ETS (Sepkovic et al., 1986; Haley et al., 1989; [10, p.241]).

Single i.v. administration of nicotine to male smokers smokers and nonsmokers results in 2 groups: one group

showing lower urinary recoveries of nicotine and cotinine in smokers vs. nonsmokers; the other group shows a similar urinary recovery of nicotine but a higher recovery of cotinine in smokers (Beckett et al., 1971b; [10, p241]).

TS and nicotine influences the pharmacokinetics of many commonly used therapeutic agents (reviewed in Jusko, 1978; Miller, 1989, 1990 [10, p.237].

Pharmacological effects of metabolites

Cotinine is pharmacologically active in animals (Borzelleca et al., 1962; Yamamoto & Domino, 1965 [sec., 9]).

shows no cardiovascular activity at levels to which cigarette smokers are generally exposed and had only weak psychological activity (Benowitz et al., 1983 [sec., 9]).

Eliminiation

When elimination of nicotine from the body is accelerated, the consumption of tobacco products may increase in order to maintain a desired level of nicotine in the body (Benowitz et al., 1990; Russel et al., 1990)

Nicotine clearance was significantly greater in nonsmokers than in smokers (1320 ml/min vs. 1070 ml/min): Jacob and Benowitz, 1993.

Nicotine clearance was faster in smokers than in nonsmokers: Kyerematen et al., 1982. (use of racemic nicotine!).

Terminal halflife in nonsmokers shorter than in smokers (122 min vs. 157 min), not significant (Jacob and Bewenowitz, 1993).

Cotinine half-life similar in smokers and nonsmokers ([0]; Curvall et al., 1990 (Cot i.v.); de Shepper et al., 1987 (Cot i.v.); Jarvis et al., 1988 (Nic oral); [0]).

Cotinine halflife slightly shorter in smokers than in nonsmokers (Kyerematen et al., 1982 (use of racemic nicotine!); [0])

Cotinine halflife considerable shorter in smokers than in non-smokers (Haley et al., 1989; [0]). Methodological problems?, see ref. [0, p.207].

Enzyme Induction/Inhibition

in vivo:

in vitro:

PB-induction leads to a 2.5-fold increase in covalent binding to rabbit liver microsome macromolecules (Shigenaga et al., 1988). Bedeutung fraglich: Was bindet an was? Wieso Rede von Alkylation? 3H-Markierung an 2'- Isotopenaustausch? Abspaltung von 3H bei metabolischer Bildung von delta-(2',5')- oder delta-(2'5')-imminium species.

Rabbit liver microsomes after PB induction metabolize S-nicotine more efficiently than microsomes from control rabbits (Shigenaga et al., 1988). Similar for the rat (Nakayama et al., 1982).

Conclusion

Interindividual variations in the pharmacokinetics of nicotine may be influenced by a wide range of endogenous as well as exogenous factors. These interindividual variations may attribute to inter-individual differences in the pharmacological response to nicotine.

References:

0 Jacob and Benowitz, 1993; in: Gorrod and Wahren,...197-218
1 Benowitz et al., 1990; in: Wonnacott et al., ...[sec., 0]
2 Russel et al., 1990: in: Wonnacott et al., ...[sec., 0]
3 Shigenaga et al., 1988; Drug Metab. Disp. 16, 397-402
4 Nakayama et al., 1982; BBRC 108, 200-205 [sec., 3]
5 Beckett et al., 1971; J. Pharm. Pharmacol. 23, 55S-61S [sec., 0]
6 Kyerematen et al., 1982; Clin. Pharmacol. Ther. 32, 769-780 [sec., 0]
7 Lee et al., 1987; Clin. Pharmacol. Ther. 41, 474-479 [sec., 0]
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9 Curvall et al., 1990; Eur. J. Clin. Pharmacol 38, 281-287
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11 Byrd et al., 1992; in: The Biology of Nicotine: Current Research Issues; Lipiello.....